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US EPA particulate matter research centers: summary of research results for 2005–2011

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Abstract The US Environmental Protection Agency funded five academic research centers in 2005 to address uncertainties in the health effects caused by airborne particulate matter (PM) as suggested by the 1998 National Research Council report, "Research Priorities for Airborne Particulate Matter." The centers employed multidisciplinary teams of epidemiologists, toxicologists, atmospheric scientists, engineers, and chemists to approach four key research themes: susceptibility to PM, biological mechanisms of PM response, exposure–response relationships, and source linkages. This review presents selected accomplishments in these categories from the past 5-year period. Publications from the centers are summarized to provide both an overview of the accomplishments to date and easy reference to much of the original literature published by the centers. Numerous investigators worked together within and across centers to investigate the relationships between atmospheric PM and health effects, including (a) the role of reactive oxygen species, inflammation, the nervous system, and the cardiovascular system, (b) particle characteristics such as size, composition, source, and temporal pattern of exposure, and (c) phenotypic and genotypic characteristics of the population that influence the level of exposure and risk in response to a given exposure.

Keywords Air pollution · Particulate matter · Exposure · Susceptibility · Source–health relationships · Acute effects · Chronic effects · Biological mechanisms · Epidemiological associations

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Abbreviations

AHR	Airway hyperresponsiveness
Al	Aluminum
APOE	Apolipoprotein E
As	Arsenic
BAL	B aggressive lymphoma
BC	Black carbon (preferred over EC, elemental carbon)
BMI	Body mass index
BP	Blood pressure
Br	Bromine
BW	Body weight
CAPs	Concentrated ambient particles
CI	Confidence interval
CNS	Central nervous system
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPZ	Capsazepine
Cr	Chromium
CRP	C-reactive protein
Cu	Copper
DC	Dendritic cell
DCFH-DA	Dichlorofluorescein diacetate
DEP	Diesel exhaust particulates
DPF	Diesel particulate filters
DTT	Dithiothreitol [assay]
EC	Endothelial cell
ECG	Electrocardiogram
eNO	Exhaled nitric oxide
EUK-134	chloro[[2,2′-[1,2-ethanediylbis[(nitrilo-κN)methylidyne]]bis[6-methoxyphenolato-κO]]]-manganese (not spelled out in the text)
GSTM1	Glutathione S-transferase M1
HBEpCs	Human bronchial epithelial cells
HDL	High-density lipoprotein
HF	High frequency
HFE	Hemochromatosis [gene]
HMEC	Human microvascular endothelial cell
HMOX-1	Heme oxygenase-1
HR	Heart rate
HRV	Heart rate variability
Hsp27	Heat shock protein 27
ICAM-1	Intercellular adhesion molecule-1
IL	Interleukin [IL-4, IL-5, IL-6]
LA	Los Angeles
LF	Low frequency
LINE	Long interspersed nucleotide element [as in LINE-1]
LPL	Lipoprotein lipase
LPS	Lipopolysaccharide
MAP	Mitogen-activated protein [kinase]
MESA Air	Multi-Ethnic Study of Atherosclerosis and Air Pollution
MI	Myocardial infarction
Mn	Manganese
Na	Sodium
NAC	*N*-acetylcysteine
NAS	Normative Aging Study
Ni	Nickel
NO_2	Nitrogen dioxide
NQO-1	NADPH quinone oxidoreductase-1
OC	Organic carbon
OVA	Ovalbumin
ox-PAPC	Oxidized 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphorylcholine
PAH	Polycyclic aromatic hydrocarbon
Pb	Lead
PM	Particulate matter
$PM_{0.25}$	Particulate matter <0.25 μm in diameter
PM_{10}	Particulate matter <10 μm in diameter
$PM_{2.5}$	Particulate matter <2.5 μm in diameter
PN	Particle number
QTc	QT interval [in ECG]
ROS	Reactive oxygen species
S	Sulfur
SAA	Serum amyloid A
sCD40L	Soluble CD40 ligand [protein]
SDNN	Standard deviation of normal-to-normal
Si	Silicon
sICAM-1	Soluble intercellular adhesion molecule-1
siRNA	Small interfering RNA
SNP	Single nucleotide polymorphism
SOD1	Superoxide dismutase 1
ST	Isoelectric period [in ECG plot]
sVCAM-1	Soluble vascular cell adhesion molecule-1
SVOC	Semivolatile organic compound
TBARS	Thiobarbituric acid reactive substances assay
TERESA	Toxicological Evaluation of Realistic Emissions Source Aerosols
TNF-α	Tumor necrosis factor-α
TRPV1	Vanilloid receptor 1
UFP	Ultrafine particle
V	Vanadium
VA NAS	Department of Veterans Affairs Normative Aging Study
VCAM-1	Vascular cell adhesion molecule-1
VEGF	Vascular endothelial growth factor
vWF	von Willebrand factor
Zn	Zinc

Introduction

In 2005, the US Environmental Protection Agency (EPA) funded the second 5 years of particulate matter (PM) research centers to continue investigating the links between airborne PM and a range of health effects as motivated by the National Research Council report "Research Priorities for Airborne Particulate Matter" (National Research Council 1998). Centers managed by Harvard University (Boston, MA), University of Rochester (Rochester, NY), and University of California, Los Angeles (Los Angeles, CA) continued from the previous 6-year funding period, while centers managed by Johns Hopkins University (Baltimore, MD) and University of California, Davis (Davis, CA) started anew. All five centers employ multidisciplinary teams of scientists and engineers to approach four key areas of uncertainty, each with their own section in this review: mechanisms, source linkages, exposure–response relationships, and susceptibility. This review summarizes selected findings from the five centers during this 5-year period of research. More details and all center publications can be found at the center web sites (U.S. EPA 2010).

Biological mechanisms of PM response

Figure 1 illustrates a primary hypothesis for the mechanism by which PM in ambient air affects human health. The mechanism is through the induction of pulmonary inflammatory responses mediated through the generation of reactive oxygen species (ROS).

PM size, composition, and reactivity—deposition, uptake, and oxidative stress

The premise that particles are able to enter and deposit in the respiratory tract is of paramount importance to PM toxicity. Exposure to ambient particles in the respiratory tract or other organ systems can lead to chemical reactions with the formation of ROS and can form covalent bonds with tissue nucleophiles.

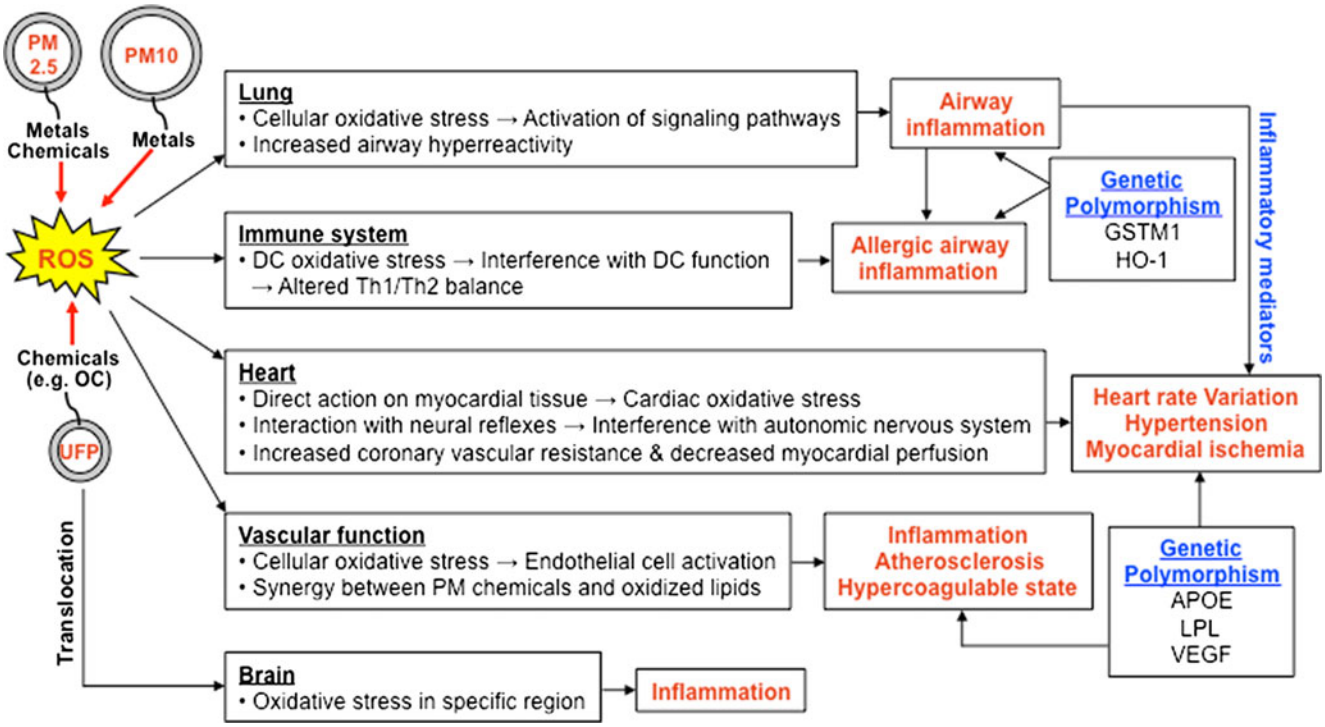

Fig. 1 Particle-induced ROS generation as a major mechanism for the adverse effects of PM in the respiratory, cardiovascular, immune, and neural systems. ROS are generated by organic chemicals (e.g., PAH and quinones) and/or transition metals associated with PM and UFP, which contain a significantly greater amount of organic chemicals than PM_{10} and $PM_{2.5}$ due to their small size and large surface area. ROS interact with the lung, immune effector cells, and the cardiovascular systems to cause cellular oxidative stress, resulting in inflammation and altered function leading to disease. Because of their extremely small size, inhaled UFP are capable of being transported from the nose, along the olfactory nerve, to the olfactory bulb, where they can also induce oxidative stress and inflammation in the brain. Genetic variation also plays an important role in determining the health effects of PM. Polymorphisms in antioxidant and phase II enzyme genes (for example, HO-1 and GSTM1) have been associated with increased susceptibility to the adverse pulmonary effects of PM, whereas polymorphisms in ApoE, LPL, and VEGF genes may render individuals more prone to the particles' cardiovascular effects. Taken together, studies undertaken by the EPA PM centers suggest that ROS production and induction of cellular oxidative stress by PM-associated organic chemicals and/or metals, combined with the particle's physical properties, are major mechanisms responsible for the diverse health effects of particulate pollutants

Assays have been developed through PM center support to quantitatively determine the capacity of PM samples to generate ROS (DiStefano et al. 2009) while also measuring the content of electrophiles generated (Shinyashiki et al. 2009). These assays can be applied to a variety of ambient and diesel exhaust particles and to vapors. Interestingly, researchers have noted that pro-oxidants and electrophiles in the vapor phase of ambient air samples have an electrophile content approximately 10 times that found in the particle phase (Eiguren-Fernandez et al. 2010).

Hatzis et al. (2006) evaluated the direct interaction of ambient particulates with protective enzymes present in oxidative stress responses. They found that copper/zinc (Cu/Zn) superoxide dismutase, manganese (Mn) superoxide dismutase, glutathione peroxidase, and glutathione reductase are consumed by interactions with particles of varying toxicities. These findings stress the potential importance of gene expression and transcription to form new enzymes in the presence of particulates. Nel et al. (2006) devised a hierarchical oxidative stress response model to more fully explain the mechanisms by which PM and its redox-active organic chemicals induce adaptive, proinflammatory and toxic cellular effects.

Deposition and uptake of particles in the respiratory tract are probably of key importance to the toxicity observed in tissue target sites and organ systems (Donaldson et al. 2008; Wegesser et al. 2009). The ability of inhaled ultrafine particles (UFP) to translocate from sites of deposition in the respiratory tract to secondary organs may directly contribute to changes found in vascular, cardiac, and central nervous system (CNS) endpoints. For example, radiolabeled ultrafine iridium particles have been observed in rats to translocate from lung surfaces through interstitial pathways, reenter the conducting airways, and eventually be cleared through the gastrointestinal tract (Semmler-Behnke et al. 2007). In these studies, alveolar macrophage clearance of UFP appears to be less efficient than for larger particles. Only a small fraction of the deposited UFP (between 0.1 and 1.0 %) is transported to secondary organs (Kreyling et al. 2009). UFP depositing in the nose have also been shown to traverse the olfactory nerve to the olfactory bulb. Ultrafine Mn oxide particles that translocate in this manner induce inflammation and oxidative stress in specific regions of the brain (Elder et al. 2006; Ngo et al. 2010).

Target: respiratory

The mechanisms by which airborne particles affect the respiratory tract have been a critical area of study in the PM centers. In particular, susceptibility of the respiratory system in compromised hosts has been of great interest. Liu et al. (2009) found that an adjuvant effect of ambient UFP on the primary immune response enhances allergic sensitization to mouse allergen ovalbumin (OVA). They correlated this adjuvant effect to particles' oxidant potential and polycyclic aromatic hydrocarbon (PAH) content. Subchronic effects of PM in the lung have further been investigated in a murine model of asthma with OVA exposure. Significant increases in airway responsiveness to acetylcholine in OVA-treated mice were noted, with Baltimore PM exposure inducing significant changes in airway hyperresponsiveness (AHR) in both naive mice (healthy) and OVA-induced asthmatic mice (susceptible). PM evoked eosinophil and neutrophil infiltration into airways, elevated B aggressive lymphoma (BAL) protein content, and stimulated secretion of Th1 cytokines (IFN-γ, interleukin (IL)-6, and tumor necrosis factor-α (TNF-α)) and Th2 cytokines (IL-4, IL-5, and eotaxin) into murine airways in both healthy and susceptible mice. PM effects on AHR and BAL eosinophil peaked at day 4 following PM exposure and declined to basal levels after 7 days. Furthermore, PM consistently induced the expression of genes involved in innate immune responses, chemotaxis, and complement system pathways. Asthmatic marker genes, such as CLCA3, TFF2, and CFB, were synergistically deregulated by PM challenge in susceptible mice (Wang et al. 2008).

Wilker et al. (2009a) assessed candidate genes for respiratory disease associated with markers of inflammation and endothelial dysfunction in elderly men. Plasma levels of circulating C-reactive protein (CRP), fibrinogen, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) were obtained from 679 participants in the Normative Aging Study (NAS). Blood samples were analyzed for 202 single nucleotide polymorphisms (SNP) in 25 candidate genes and included both haplotype tag SNPs and functional SNPs. In analyzing the relationship between biomarker level and genotype adjusted for age and body mass index (BMI), SNPs in the CRHR1, ITPR2, and VDR genes showed significant associations. These results suggest that genes thought to play a role in the pathogenesis of asthma and chronic obstructive pulmonary disease (COPD) may influence levels of serum markers of inflammation and endothelial dysfunction via SNP associations that have not previously been associated with cardiovascular disease (Wilker et al. 2009b).

A variety of inhalation studies in laboratory animals continue to confirm the ability of particle size and composition to influence acute and subacute impacts on the lungs (Smith et al. 2006; Pinkerton et al. 2008; Wegesser et al. 2009; den Hartigh et al. 2010; Zhong et al. 2010). The importance of a lag time in observed PM response (Smith et al. 2006) as well as age and synergism between PM components in neonates and adults (Pinkerton et al. 2008; Wegesser et al. 2009; Zhong et al. 2010) emphasizes the importance of particle size, concentration, and composition in respiratory outcomes.

Target: immune system

The adjuvant effect of UFP may be explained, at least partially, by a particle's effect on antigen presenting dendritic cells (DC). Chan et al. (2006) demonstrated that pro-oxidative diesel exhaust particulates (DEP) induce oxidative stress in DC and interfere with lipopolysaccharide (LPS)-induced Th1-promoting response pathways. Zhao et al. (2009) found that Baltimore PM induced cyclooxygenase (COX)-2 expression and IL-6 release through both an ROS-dependent NF-κB pathway and an ROS-independent C/EBPβ pathway in human bronchial epithelial cells (HBEpCs) in culture. Pretreatment with *N*-acetylcysteine (NAC), EUK-134, or ROS scavengers attenuated PM-induced ROS production, COX-2 expression, and IL-6 release. PM-induced ROS was of mitochondrial origin, as evidenced by increased oxidation of the mitochondrially targeted hydroethidine to hydroxyethidium by reaction with superoxide. Exposure of HBEpCs to PM stimulated phosphorylation of NF-κB and C/EBPβ, while the NF-κB inhibitor, Bay11–7082, or C/EBPβ small interfering RNA (siRNA) attenuated PM-induced COX-2 expression and IL-6 release. Furthermore, NAC or EUK-134 attenuated PM-induced activation of NF-κB; however, NAC or EUK-134 had no effect on phosphorylation of C/EBPβ. In addition, inhibition of COX-2 partly attenuated PM-induced prostaglandin E2 and IL-6 release.

Target: cardiac

Rhoden et al. (2005) used a rat model of unilateral denervation of the lung to explore the role of PM-induced oxidant stress in altering cardiac function via a complex combination of sympathetic and parasympathetic neural responses. After instillation of either saline solution (control) or urban air particles to denervated lung, cardiac and pulmonary oxidants were measured using in vivo chemiluminescence. Cardiac responses to PM were significantly attenuated in denervated animals, suggesting that pulmonary reflexes are important in the development of cardiac damage by PM. Ghelfi et al. (2008) investigated the effect of blockade of vanilloid receptor 1 (TRPV1) on concentrated ambient particles (CAPs)-induced cardiac oxidative stress and dysfunction in a rat model of inhalation exposure. Capsazepine (CPZ), a selective antagonist of TRPV1, was given through intraperitoneal injection or as an aerosol immediately before exposure to CAPs. Control and CPZ-treated rats were exposed to filtered air or CAPs (218±23 mg/m^3). CPZ decreased CAPs-induced cardiac oxidative stress measured by in situ chemiluminescence, tissue edema, and lipid peroxidation as measured by thiobarbituric acid reactive substances assay (TBARS). CAPs-related changes in cardiac rhythm and electrocardiogram (ECG) morphology were prevented by CPZ. These data suggest that CAPs exposure alters action potentials, leading to changes in conduction velocity and ventricular repolarization, and that triggering of TRPV1-mediated autonomic reflexes in the lung is essential for the observed changes in cardiac rhythms.

Tonne et al. (2009) showed that long-term exposure to vehicular traffic particles is associated with an increase in the occurrence of acute myocardial infarction (MI). Cases of acute MI were more exposed to traffic and traffic particles compared to controls. An interquartile range increase in modeled traffic particles was associated with a 10 % (95 % confidence interval (CI), 4, 16 %) increase in the odds of acute MI.

In this report, the term black carbon (BC) is used to refer to the elemental carbon content of PM. von Klot et al. (2009) showed that, when the effect of estimated BC on the long-term mortality of patients discharged after MI was analyzed using a Cox proportional hazards model (controlling for a variety of demographic, medical history, and clinical variables), chronic traffic-related particulate air pollution was associated with increased mortality in hospital survivors of acute MI after the second year of survival.

Chuang et al. (2008) assessed PM air pollution as a risk factor for isoelectric period (ST segment) depression in patients with coronary artery disease. Elevation in PM of <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and BC levels predicted depression of half-hour-averaged ST segment levels. An interquartile increase in the previous 24-h mean BC level was associated with a 1.50-fold increased risk of ST segment depression ≥0.1 mm (95 % CI, 1.19 to 1.89) and a −0.031 mm (95 % CI, −0.042 to −0.019) decrease in half-hour-averaged ST segment level (continuous outcome). Effects were greatest within the first month after hospitalization and for patients with MI during hospitalization or with diabetes. Therefore, the risk of pollution-associated ST segment depression may be greatest in those with myocardial injury in the first month after the cardiac event. ST segment depression of ischemic type (≥1.0 mm) was also associated with increased exposure to $PM_{2.5}$ and BC in patients with coronary artery disease in a panel study in the Los Angeles (LA) air basin (Delfino et al. 2011). The findings of the above studies suggest that traffic-related air pollutants may carry important chemical components that result in cardiac ischemia.

Bartoli et al. (2009) measured the effect of CAPs on myocardial blood flow and perfusion using fluorescent microspheres in a canine model of myocardial ischemia. CAPs exposure decreased total myocardial blood flow during coronary artery occlusion by 0.12 mL/min/g ($p<0.001$) and was accompanied by a 13 % ($p<0.001$) increase in coronary vascular resistance. CAPs effects on myocardial blood flow were significantly more pronounced in myocardium within or near the ischemic zone versus more remote

myocardium (p interaction<0.001). Robust correlations were found with particles associated with vehicular traffic. These results suggest that PM exacerbates myocardial ischemia by increased coronary vascular resistance and decreased myocardial perfusion and provides an explanation for both the increases in acute MI in human studies and the findings of long-term cardiac mortality found in those chronically exposed to traffic pollution.

In a study by Ramos-Bonilla et al. (2010), AKR/J inbred mice were exposed to ambient air for 6 h/day for 40 weekdays to study cardiac outcomes. Exposure to ambient PM was closely monitored in conjunction with copollutants ozone, carbon monoxide, and nitrogen dioxide (O_3, CO, and NO_2, respectively). Significant associations were observed at different time lags, suggesting that multiple cardiac pathophysiological mechanisms could be involved. CO was significantly associated with declines in heart rate (HR) and heart rate variability (HRV). PM was significantly associated with declines in HRV and body weight (BW), and NO_2 was significantly associated with declines in HR. Some significant associations occurred in the same day (PM and HRV, PM and BW, CO and HR), while others were delayed by 1 to 3 days (CO and HR, CO and HRV, NO_2 and HR, PM and HRV). Alterations in cardiac effects seen were also dependent on the advanced age of the mice. Both the immediate and delayed timing of these outcomes suggests that air pollutants follow multiple pathophysiological pathways to generate cardiac disease. This study also illustrates cardiac alterations in mice associated with real-world air pollution exposures at concentrations that mimic human exposure.

Source apportionment analyses also support the importance of traffic-related and combustion-related PM in cardiac effects (Yue et al. 2007). Further studies in mice have demonstrated that combustion-generated UFP can induce neuroplasticity of cardiac vagal neurons as a potential mechanism contributing to the cardiovascular consequences associated with PM exposure seen in humans (Pham et al. 2009).

Target: vascular

Using CAPs, studies have demonstrated that ambient PM (UFP versus $PM_{2.5}$) promotes atherosclerosis, interferes with plasma high-density lipoprotein (HDL) anti-inflammatory activity, and induces systemic oxidative stress in apoE-null mice. UFPs compared with $PM_{2.5}$ were found to be more proatherogenic, to exert the strongest pro-oxidative effects, and to be associated with the largest decrease in HDL protective activity (Araujo et al. 2008). Studies using subacute, repeated exposure to CAPs demonstrate both a systemic proinflammatory and procoagulant response to inhaled fine and ultrafine PM, suggesting a role for platelet activation in the cardiovascular and respiratory effects of PM air pollution (Wilson et al. 2010).

PM exposure may also affect vascular function via systemic inflammation. Patients with coronary artery disease showed increases in CRP and serum amyloid A (SAA) in association with exposure to both UFPs and larger PM (Rückerl et al. 2006). In another study of patients with coronary artery disease, biomarkers of systemic inflammation including IL-6 were positively associated with BC, primary organic carbon (OC), and quasi-UFP <0.25 μm in diameter. This result was consistent with associations for particle number (PN) concentrations (Delfino et al. 2009, 2010a). Rückerl et al. (2006) also found evidence for endothelial activation, with increases in von Willebrand factor (vWF) and ICAM-1. Blood markers also provided evidence for an effect of PM on a hypercoagulable state (Rückerl et al. 2006) and platelet activation (Delfino et al. 2009; Rückerl et al. 2007).

Patients with COPD showed increases in E-selectin but decreases in vWF, with no changes in CRP or SAA (Hildebrandt et al. 2009). Fibrinogen increased, but there were no effects on prothrombin fragment 1+2. Interestingly, COPD patients showed a decrease in blood polymorphonuclear leukocytes and increases in monocytes associated with UFP exposure (Brüske-Hohlfeld et al. 2010).

Human clinical studies suggest that inhalation of BC UFP has transient effects on vascular function in both the pulmonary (Pietropaoli et al. 2004; Frampton et al. 2006) and systemic (Shah et al. 2008) vascular beds. In people with type 2 diabetes, UFP inhalation increased markers of platelet and endothelial activation (Stewart et al. 2010), without altering coagulation factors.

Observed increases in blood pressure (BP) have been controversial. Mordukhovich et al. (2009) observed positive associations between BP and BC, but not between BP and $PM_{2.5}$, and found no evidence of effect modification of the association between BC and BP by gene variants related to antioxidant defense. Delfino et al. (2010b) found positive associations between hourly BP measured with ambulatory monitors and hourly to multiday averages of BC, OC (especially the combustion-related fraction), and $PM_{2.5}$. Studies at the Harvard center, which included controlled human exposures at the University of Toronto, showed that CAPs plus ozone increased diastolic BP (Fakhri et al. 2009). Analyses of additional data from Toronto showed that diastolic BP significantly increased (2.9 and 3.6 mmHg) only during particle-containing exposures in association with PM concentration and reductions in HVR (Brook et al. 2009). Flow-mediated dilatation significantly decreased (2.0 and 2.9 %) only 24 h after particle-containing exposures in association with PM concentration and increases in blood TNF-α. PM, not ozone, was responsible for increasing diastolic BP during air pollution inhalation, most plausibly

by instigating acute autonomic imbalance. Only particles from urban Toronto additionally impaired endothelial function, likely via slower proinflammatory pathways.

Bartoli et al. (2009) studied acute hemodynamic mechanisms related to 5-h exposures to CAPs or filtered air in canines (n=13). Animals were exposed either to CAPs (mass concentration, 356.0±91.2 μg/m^3 [mean±SD]) or filtered air in a crossover protocol (53 CAPs days, 63 filtered air days). In a subset of animals, baroreceptor reflex sensitivity was measured before and after exposures (n=10, 19 CAPs days, 19 filtered air days) or without and with α-adrenergic blockade (n=7, 16 CAPs days, 15 filtered air days). CAPs exposure increased systolic BP (2.7± 1.0 mmHg, p=0.006), diastolic BP (4.1±0.8 mmHg; p< 0.001), mean arterial pressure (3.7±0.8 mmHg; p<0.001), HR (1.6±0.5 bpm; p<0.001), and HR–BP product (539± 110 bpm mmHg; p<0.001) and decreased pulse pressure (−1.7±0.7 mmHg, p=0.02). These changes were accompanied by a 20±6 ms/mmHg (p=0.005) increase in baroreceptor reflex sensitivity after CAPs versus filtered air exposure. The finding that increased baroreceptor reflex sensitivity occurred during particulate exposure suggests relatively early compensation for or correction of BP increases, which may explain some of the divergent findings in previously published studies. To test whether CAPs-induced increases in arterial BP were mediated by acute, peripheral vasoconstriction, oral prazosin, a selective α1-adrenergic antagonist with minimal effect on cardiac function, was administered. During α-adrenergic blockade, CAPs exposure was associated with smaller, nonsignificant increases in arterial BP as compared to CAPs-exposed animals without α-adrenergic blockade. These results suggest that an increase in α-adrenergically mediated peripheral vascular resistance may be responsible for air pollution-induced hypertensive response.

Baltimore PM also mediated pulmonary endothelial cell (EC) permeability increases and EC barrier disruption. PM induced significant dose-dependent (10–100 μg/ml) and time-dependent (0–10 h) EC barrier disruption. Exposure of human lung EC to PM resulted in significant ROS generation that was directly involved in PM-mediated EC barrier dysfunction, as shown by the observation that NAC (5 mM) pretreatment abolished both ROS production and barrier disruption induced by PM. Furthermore, PM induced both p38 mitogen-activated protein (MAP) kinase activation and heat shock protein 27 (Hsp27) phosphorylation, events that were both attenuated by NAC. Additionally, PM-induced EC barrier disruption was partially prevented by the p38 MAP kinase inhibitor SB203580 (10 μM) as well as by reduced expression of either p38β MAP kinase or Hsp27 (using siRNA methods). These findings support a novel mechanism for PM-induced lung dysfunction and adverse cardiopulmonary outcomes (Wang et al. 2010).

Target: autonomic/brain

Although neurocognitive effects of exposure to PM do not directly relate to mechanism, they represent important outcomes. Chen and Schwartz (2009) identified neurobehavioral effects associated with long-term exposure to ambient PM and ozone in adults. In age-adjusted and sex-adjusted models, PM predicted reduced CNS functions, but the association disappeared after adjustment for sociodemographic factors. In models adjusting for demographics, socioeconomic status, lifestyle, household and neighborhood characteristics, and cardiovascular risk factors, ozone predicted high scores in a symbol–digit substitution test (SDST) and a serial digit learning test (SDLT), but not in a simple reaction time test. Each 10-ppb increase in annual ozone was associated with increased SDST and SDLT scores by 0.16 (95% CI, 0.01, 0.23) and 0.56 (95% CI, 0.07, 1.05), equivalent to 3.5 and 5.3 years of aging-related decline in cognitive performance, respectively. This study provides the first epidemiological data supporting adverse neurobehavioral effects of air pollutants in adults.

Animal studies also implicate combustion-generated UFPs in inducing changes in the signaling and neuroplasticity of cardiac vagal neurons. These changes contribute to cardiovascular consequences like those observed in human PM exposure (Pham et al. 2009).

Target: genetic/epigenetic

In human studies, Schwartz et al. (2005) found that reduced defenses against oxidative stress due to glutathione S-transferase M1 (GSTM1) deletion modify the effects of $PM_{2.5}$ on HRV in a cross-sectional analysis of the NAS cohort. This observation has been extended to include a longitudinal analysis with more subjects and examination of the GT short tandem repeat polymorphism in the heme oxygenase-1 (HMOX-1) promoter (Chahine et al. 2007). There was no association in subjects with GSTM1, whereas there was a significant association with standard deviation of normal-to-normal (SDNN) intervals, high frequency (HF), and low frequency (LF) in subjects with the deletion. These analyses suggest oxidative stress is an important pathway for the autonomic effects of particles.

Baccarelli et al. (2009) assessed the effect of PM pollution on epigenetic mechanisms in cardiovascular disease by determining DNA methylation in heavily methylated sequences with high representation throughout the human genome. DNA methylation of long interspersed nucleotide element (LINE)-1 and Alu repetitive elements was measured by quantitative polymerase chain reaction–pyrosequencing of 1,097 blood samples from 718 elderly participants in the Boston area NAS. LINE-1 methylation decreased after recent exposure to higher BC (β=−0.11;

95 % CI, −0.18 to −0.04; p=0.002) and $PM_{2.5}$ (β=−0.13; 95 % CI, −0.19 to −0.06; p<0.001 for the 7-day moving average). In two-pollutant models, only BC, a tracer of traffic particles, was significantly associated with LINE-1 methylation (β=−0.09; 95 % CI, −0.17 to −0.01; p=0.03). No association was found with Alu methylation (p>0.12). Although decreased repeated-element methylation after exposure to traffic particles was found, it remains to be determined whether decreased methylation mediates exposure-related health effects.

Madrigano et al. (2010) examined the association between air pollution, obesity, genes, and cellular adhesion molecules in a longitudinal study of 809 participants in the NAS (1,819 total observations). The study used mixed-regression models to examine the association of $PM_{2.5}$ and BC with serum concentrations of soluble ICAM-1 and soluble VCAM-1 (sVCAM-1), markers of endothelial function and inflammation. Genes selected for analysis were either related to oxidative stress, endothelial function, lipid metabolism, or metal processing. BC during the 2 days prior to blood draw was significantly associated with increased sVCAM-1 (4.5 % increase per 1 μg/m^3; 95 % CI, 1.1, 8.0). Neither pollutant was associated with soluble ICAM-1. Larger effects of BC on sVCAM were seen in subjects with obesity (p=0.007) and who were GSTM1-null (p=0.02). Thus, BC is associated with markers of endothelial function and inflammation. Genes related to oxidative defense may modify this association.

Ren et al. (2010a) assessed lipid-related and endothelial-related genes, ambient PM, and HVR in the Veterans Affairs NAS (VA NAS). To determine if exposures to ambient particles act on autonomic function via lipid/endothelial metabolism pathways, they evaluated whether or not the effects of $PM_{2.5}$ on HRV were modified by gene polymorphisms related to those pathways. They used HRV and gene data from the NAS and $PM_{2.5}$ from a monitor located a kilometer from the examination site. They then used a mixed model to investigate the associations between $PM_{2.5}$ and repeated measurements of HRV by gene polymorphisms APOE, LPL, and VEGF, adjusting for potential confounders chosen a priori. A 10-μg/m^3 increase of $PM_{2.5}$ in the 2 days before the examination was associated with 3.8 % [95 % CI, 0.2, 7.4 %], 7.8 % [95 % CI, 0.4, 15.3 %], and 10.6 % [95 % CI, 1.8, 19.4 %] decreases of SDNN intervals, LF, and HF, respectively. Overall, carriers of wild-type APOE, LPL, and VEGF genes had stronger effects of particles on HRV compared to those with heterozygous or homozygous types. Variations of LPL-N291S, LPL-D9N, and APOE-G113C significantly modified the effects of $PM_{2.5}$ on HRV. Associations between $PM_{2.5}$ and HRV were modified by gene polymorphisms of APOE, LPL, and VEGF.

Gong et al. (2007) used human microvascular endothelial cells (HMEC) to study the combined effects of a model air pollutant, DEP, and oxidized 1-palmitoyl-2-arachidonyl-*sn*-glycero-3-phosphorylcholine (ox-PAPC) on genome-wide gene expression. DEP and oxidized phospholipids were found to affect synergistically the expression profile of several gene modules that correspond to pathways relevant to vascular inflammatory processes such as atherosclerosis.

Source linkages

This section presents results from center studies that link PM toxicity to particle physicochemical characteristics, source types, and atmospheric processes. These findings potentially can be used to better target regulatory strategies.

Linking PM health impacts to sources

Cheung et al. (2009) characterized diesel vehicles without diesel particulate filters (DPF) and biodiesel vehicles as having the highest PM mass emissions. These vehicles also had the highest content of carcinogenic PM compounds such as PAH. These findings also indicated that the use of DPF or cleaner fuel (gasoline) may be far more effective in reducing PAH emissions than the use of biodiesel. The semivolatile organic compound (SVOC) components of PM emitted from modern diesel engines equipped with after-treatment control technologies account for over 80 % of the redox activity of the emitted PM (Biswas et al. 2009). Thus, the SVOC particle fraction is more oxidative than the refractory particles. Recent studies have suggested a decline in PM oxidative activity with increasing atmospheric dilution (Biswas et al. 2009).

Verma et al. (2009a) investigated the impacts of the October 2007 Southern California wildfires. Both the water-soluble OC concentrations and the redox PM activity, measured by the dithiothreitol (DTT) assay, were higher during the fire events as compared to postfire concentrations.

Transformations from source to receptor

Emissions undergo a variety of physicochemical transformations during their transport from sources to receptors, resulting in the formation of secondary inorganic and organic PM species. Recent center research indicates that secondary particles are more toxic than primary ones. Venkatachari et al. (2005, 2007) have used dichlorofluorescein diacetate (DCFH-DA) to measure PM ROS activity in Rubidoux, CA and New York City. Cho et al. (2005) have used DTT assay to examine the redox activity of PM collected in the LA Basin. In addition, Zhang et al. (2008) have adapted the DCFH-DA procedure to assess the amount of endogenous ROS formed by macrophage cells in the presence of particles.

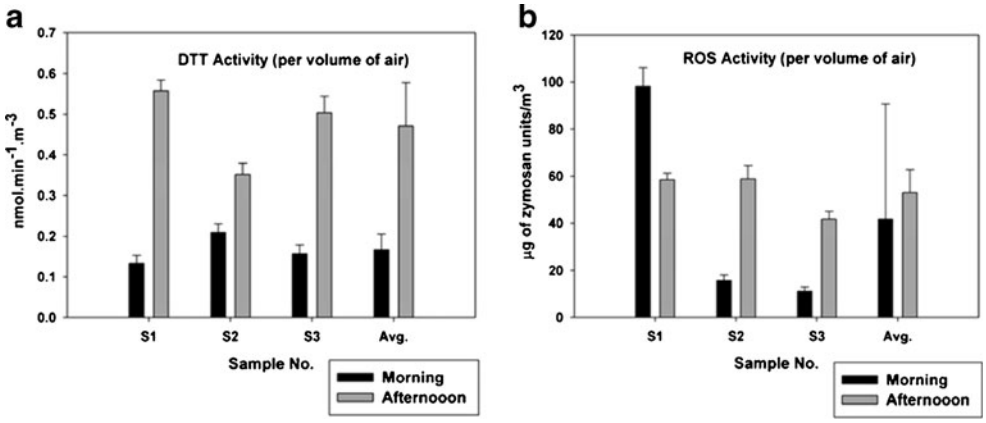

Fig. 2 DTT (*left*) and ROS (*right*) measured for morning (fresh) and afternoon (aged) particles

Verma et al. (2009b) showed that aged UFP in LA exhibited greater DTT activity and increased endogenous ROS as compared to fresh UFP. Figure 2 shows the DTT (left) and ROS (right) measured for morning (fresh) and afternoon (aged) particles. Strong correlations are observed between these redox species and secondary constituents and some metals.

The Toxicological Evaluation of Realistic Emissions Source Aerosols (TERESA) study was conducted at three US coal-fired power plants to investigate the potential toxicological effects of primary and photochemically aged (secondary) particles using in situ stack emissions. The exposure system successfully simulated chemical reactions that power plant emissions undergo in a plume during transport from the stack to receptor areas (Ruiz et al. 2007a, b). The effects of simulated aged particles are discussed in a series of TERESA papers (Godleski et al. 2011; Diaz et al. 2011; Lemos et al. 2011; Wellenius et al. 2011). These studies found that the most significant responses occurred in the more complex oxidized scenarios (Fig. 3), supporting the hypothesis that photochemically aged particles are more toxic than primary particles. These responses included increases in in vivo chemiluminescence of the heart and the lung, change in breathing patterns, increases in total cell count and macrophage number on bronchoalveolar lavage, and increases in premature ventricular heart beats in the MI model. Thus, there is substantial evidence that processes involved in the aging of particles produces oxidized OC as well as ROS (Docherty et al. 2005; Chen and Hopke 2009a, b, 2010). In limited toxicological studies, it appears that this additional ROS has measured impacts on animal models.

Source health effects

PM center-based research has shown that estimates of the health effects of PM vary substantially across communities and seasons. Part of this heterogeneity may be explained by differences in PM sources and composition.

Studies have examined relationships between $PM_{2.5}$ constituents and health effects. Bell et al. (2007a) analyzed speciation data from 187 US counties and identified 7 constituents that account for the most $PM_{2.5}$ mass (BC, OC, NH_4^+, NO_3^-, SO_4^{2-}, Si, and Na). Peng et al. (2009) used the same exposure data to discover associations between same-day emergency room admissions for cardiovascular disease and BC and between admissions for respiratory emergencies and OC. Bell et al. (2009) reported associations between short-term cardiovascular and respiratory hospitalizations and county-specific vanadium (V), BC, and nickel (Ni) levels. Similar Ni and V effects were found in a national mortality study (Dominici et al. 2007). However, the exclusion of three New York City counties diminished the apparent effect.

CAPs have been used to explore mechanisms of PM injury. In a canine model of myocardial ischemia, increases in CAPs mass and number and BC concentrations were associated with decreases in myocardial blood flow and increases in coronary vascular resistance during coronary artery occlusion (Bartoli et al. 2009).

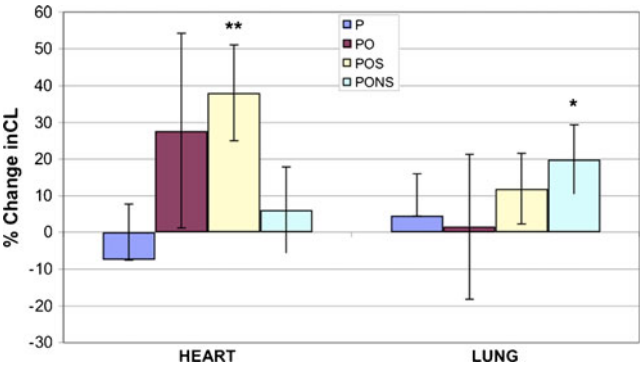

Fig. 3 Percentages of change in heart and lung chemiluminescence (a measure of ROS in tissues) for four scenarios in three power plants. *P* primary particles, *PO* oxidized PM, *POS* oxidized PM+organics, *PONS* oxidized neutralized PM+organics. *$p<0.05$, **$p<0.01$

Sources and exposure modeling

PM center researchers explored several source contributions to UFP to establish models. Riddle et al. (2008) measured molecular markers in size-resolved particle fractions yielding size-resolved source apportionments in locations throughout California (Minguillón et al. 2008; Kleeman et al. 2009). Motor vehicle exhaust dominates UFP near roadsides (Riddle et al. 2008; Fruin et al. 2008) and in traffic-intensive urban areas such as LA (Minguillón et al. 2008). Contributions from regional sources dominate UFP at locations away from roadways in regions with more typical traffic density (Kleeman et al. 2009). Traffic-generated UFP were efficiently transported to the indoor environment in Southern California (Arhami et al. 2010).

PM investigators used satellite sensing to establish particle spatial and spatiotemporal models. Liu et al. (2009) used satellite measurements to estimate $PM_{2.5}$ mass in rural/suburban areas. The spatial profiles of annual $PM_{2.5}$ in Massachusetts, Connecticut, and Rhode Island (Fig. 4, left) were estimated using data from the Moderate-Resolution Imaging Spectroradiometer (MODIS) satellite. The regional background was 10 μg/m^3, suggesting that a large fraction of PM is transported to the region. Suburban and urban areas showed higher levels by approximately 2.0 μg/m^3. The higher urban levels are due mostly to local traffic. Independent results from a BC spatiotemporal model (Fig. 4, right) show corresponding spatial gradients in traffic exposures across Eastern Massachusetts (Gryparis et al. 2007). Both methodologies and models can be critical in assessing population exposures for studies examining the health impacts of local and transported particles.

Exposure–dose–response relationships

The individual components of the exposure–dose–response paradigm are shown in Fig. 5. Ideally, detailed knowledge about the individual components would be needed to establish the cause of an observed effect.

For example, investigators have provided evidence on the relation between exposure to inhaled UFP, dose translocated to the CNS, and effects in the CNS from the biologically effective dose. This relationship was determined in a rat inhalation study designed to demonstrate the translocation of inhaled laboratory-generated UFP (a mixture of Mn oxides) from the upper respiratory tract to the CNS. Elder et al. (2006) characterized the exposure in terms of particle size and size distribution, mass and number concentration, and chemical composition. The investigators then observed the retained doses in different regions of the respiratory tract and in different parts of the CNS, along with neuroinflammatory responses. They confirmed a translocation pathway from the nose to the CNS via the olfactory nerve. The translocation resulted in 3.5-fold higher Mn concentrations in the olfactory bulb compared to twofold higher levels in the lung after 11 days of exposure at 4 h/day. Some other brain regions also showed significantly increased Mn. Significant inflammatory responses were seen in those brain regions that showed increased Mn levels: an eightfold increase of TNF-α mRNA and a 30-fold increase of TNF-α in the olfactory bulb, along with lower increases in other brain regions with smaller increases in Mn levels. No indications of pulmonary inflammation were observed.

This study shows that exposure–dose–response relationships are very different for the primary organ of

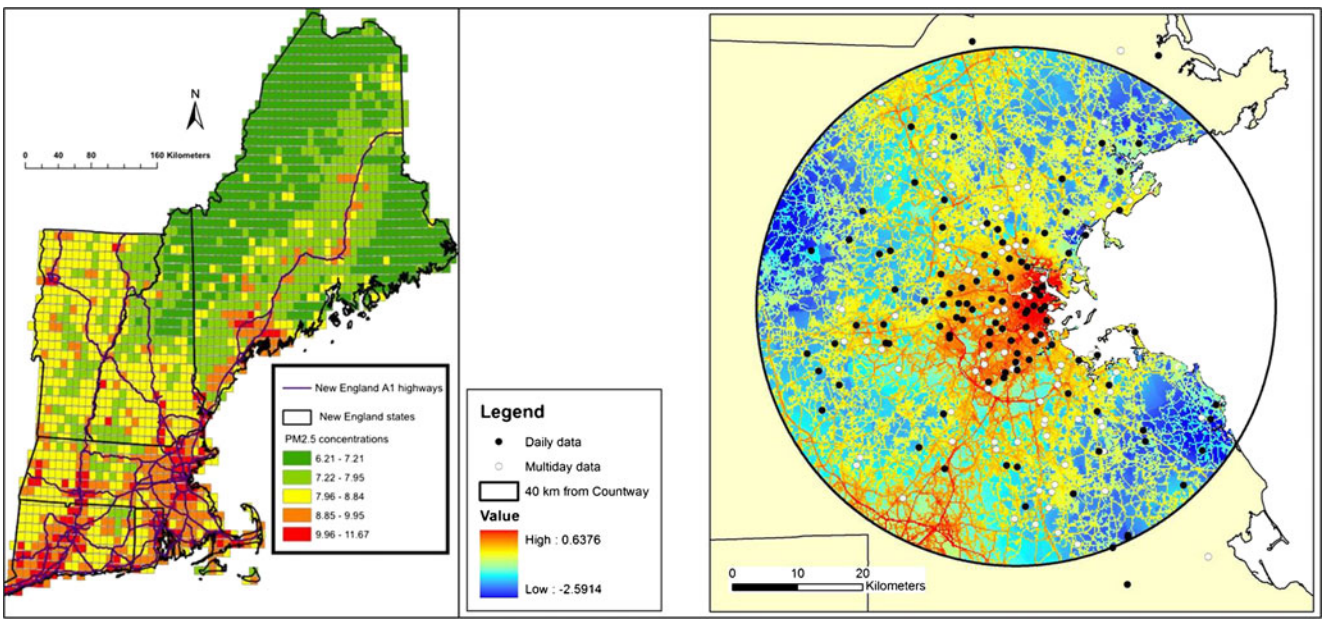

Fig. 4 $PM_{2.5}$ levels in the New England (*left*) and BC levels in greater Boston (*right*)

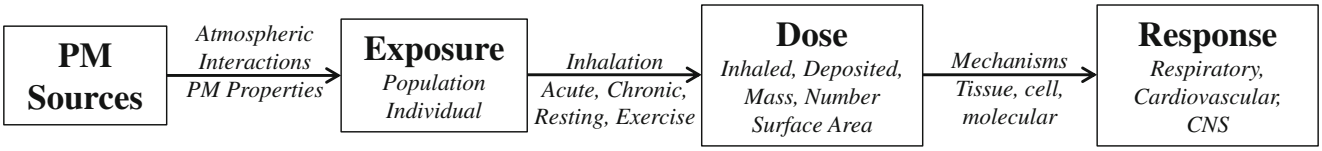

Fig. 5 Components of the exposure–dose–response paradigm

entry (in this case, the respiratory tract) and for secondary organs involving translocation/disposition of UFP. A presumed pathway of PM-induced secondary effects such as extrapulmonary inflammation has been via mediator release following inflammation in the lung. However, the olfactory bulb experiments illustrate an alternate direct route.

Obviously, similar detailed dosimetric information cannot be obtained in epidemiological or controlled clinical studies. However, in clinical studies, doses can be estimated through measurement of breathing parameters combined with knowledge about physicochemical properties of airborne PM. These estimates can help establish a more complete exposure–dose–response relationship and causality. In epidemiological studies, researchers can estimate inhaled or deposited doses by combining measures of PM concentrations from ambient area or personal monitors with predictive particle deposition models in the lung. The biologically effective dose (the dose responsible for toxic effects) will vary depending on particle composition and size fraction and may differ substantially from the overall mass of PM (Ayres et al. 2008). Thus, controlled clinical studies can complement toxicological animal and in vitro studies to provide valuable information that can confirm hypotheses and support epidemiological findings.

The method and source of data used to determine exposure–dose–response relationships vary depending on the following considerations:

- whether the interest is in acute health outcomes and short-term exposures or in chronic health outcomes and long-term exposures;
- whether the outcome is an intermediate endpoint, clinical morbidity, or mortality;
- whether the target organ system is the primary organ of entry (typically the respiratory tract) or secondary organs;
- whether epidemiological cohort or clinical studies are performed.

The following discussion focuses primarily on epidemiologic and some controlled exposure studies that have been used to assess relations across all of these dimensions. This section highlights major research findings for selected PM properties and selected health outcomes. Population characteristics and behavior that are important determinants of the dose and of the type and magnitude of air pollution exposure have been reviewed elsewhere (Sioutas et al. 2005).

Exposure–dose–response in human experimental and panel studies

Oxidative stress may play a central role in the respiratory and cardiovascular effects of air pollution. As illustrated in Fig. 1, experimental data show that redox-active PM components (especially in UFP) lead to the production of ROS in various cells in the lungs, blood, and vascular tissues. ROS production is followed by oxidative stress, which can lead to increased airway and systemic inflammation and adverse cardiovascular responses when antioxidant defenses are overwhelmed (Ayres et al. 2008; Utell et al. 2002). Furthermore, PM center investigators have shown that electrophilic properties of PM-related chemicals have the potential to covalently modify critical proteins (Shinyashiki et al. 2008, 2009), including antioxidant enzymes, which could result in increased oxidative stress and other effects. Epidemiologic data supporting this evidence are limited. Data include the result of cohort studies of antioxidant enzyme activity (Delfino et al. 2008, 2009, 2010a) and studies examining effect modification of responses to air pollutant exposures by variants in oxidative stress-related genes, as discussed in the "Susceptibility" and "Biological mechanisms of PM response" sections.

Epidemiologic data from cohort studies also support a proinflammatory effect of air pollution, especially combustion-related particles. A panel study in Erfurt, Germany of 57 male patients with coronary heart disease found increased levels of CRP for all particle size fractions including UFP (Rückerl et al. 2006). Zeka et al. (2006) found that both BC and PN increased inflammation and thrombotic activity. The PN finding suggests that UFPs are a potentially important particle size. Effects were strongest for subjects older than 78 years, individuals with chronic proinflammatory states (as shown for obese individuals), and individuals with reduced defenses to ROS (as shown for people with the GSTM1-null genetic polymorphism or in nonstatin users).

Additional information pointing to the importance of UFPs comes from a cohort of 60 subjects with a history of coronary artery disease living in four retirement communities in the LA air basin (Delfino et al. 2008, 2009).

Using 12 weekly repeated measures of circulating biomarkers of effect and outdoor community air pollutants, investigators found that the strongest positive associations of biomarkers of systemic inflammation (for example, IL-6) with size-fractionated particle mass was for the quasi-UFP fraction <0.25 μm in diameter ($PM_{0.25}$), which was consistent with positive associations for PN. Additional supportive data from these cohort study subjects with ambulatory ECGs showed that the only positive association with ST segment depression of the ischemic type (≥1.0 mm) with PM mass fraction was for $PM_{0.25}$ (Delfino et al. 2011).

In the same cohort study, Delfino et al. (2008, 2009) assessed potential differences in association from primary versus secondary organic aerosols by estimating two fractions of total $PM_{2.5}$ OC (primary OC and secondary OC, respectively) (Polidori et al. 2007). They showed that associations of biomarkers (plasma IL-6, TNF-α receptor II, soluble platelet selectin, erythrocyte glutathione peroxidase-1, and Cu,Zn-superoxide dismutase) with total OC were attributable to the primary OC fraction, not the secondary fraction. Positive associations were also more strongly positive for primary than for secondary OC in an analysis of the relation of $PM_{2.5}$ OC to hourly ambulatory BP measured over 10 days in the same cohort (Delfino et al. 2010b). Similar to other PM center panel studies (Hildebrandt et al. 2009; Mordukhovich et al. 2009; Wilker et al. 2009b, 2010), all biomarker and BP associations were strongest for multiday moving averages of air pollutants, suggesting that cumulative exposure is an important determinant of cardiovascular response. Reinforcing this view, the LA cohort study showed that the strongest positive associations with ST segment depression of the ischemic type (≥1.0 mm) were for primary OC, including 1-h through 4-day averages, which had the largest estimates (Delfino et al. 2011). These results demonstrate both very acute and longer-term exposure–response relations, potentially involving different mechanisms.

Delfino et al. (2010a) further characterized biomarker associations by assaying chemical components from extracts of $PM_{0.25}$ filters. Indoor and outdoor PAH, followed by hopanes (tracers of emissions from diesel and gasoline vehicles), were most strongly positively associated with biomarkers of inflammation. They were also able to link PAH exposures to vehicular traffic by using chemical tracers in source apportionment models (Arhami et al. 2010; Delfino et al. 2010a). The PAH content of PM, along with other SVOCs, is expected to be important in oxidative stress responses, as discussed in the "Biological mechanisms of PM response" section.

There is limited data in human populations on the differential effects of primary and secondary organic aerosols. Recent results from the LA cohort study support the hypothesis that the effects of particles on airway inflammation and on systemic inflammation differ by particle composition (Delfino et al. 2010c). Organic components related to the primary combustion of fossil fuel were more strongly and significantly associated with systemic inflammation (evidenced by the presence of IL-6), whereas organic components related to secondary photochemical aging of particles were more strongly and significantly associated with airway inflammation (exhaled nitric oxide [eNO]). These results serve as an additional example of the differences in the biologically effective dose of particle components by target organ (see Fig. 5). An in vitro measure of the overall oxidative potential of particles in collected air samples was associated with both types of inflammation, supporting the importance of ROS at multiple target sites in the body (see Fig. 1).

Overall results from the PM center cohort studies suggest that UFP and primary emission sources of PM organic chemicals, especially from traffic, lead to increased systemic inflammation and thrombosis (Delfino et al. 2008, 2009, 2010a; Hildebrandt et al. 2009; Zeka et al. 2006), oxidative stress, homocysteine levels (Park et al. 2008), elevations in BP (Delfino et al. 2010b; Mordukhovich et al. 2009; Wilker et al. 2009b, 2010), ECG ST segment depression (Chuang et al. 2008; Delfino et al. 2011), supraventricular and ventricular runs of tachycardia (Berger et al. 2006), and impaired peak forearm blood during reactive hyperemia and lower venous nitrate levels (Shah et al. 2008). These intermediate endpoints are themselves risk factors for MI, heart failure, and stroke. Therefore, such effects may be partly behind reported cardiovascular morbidity and mortality associations in the time series studies discussed below.

In order to obtain information about dose-related cardiovascular effects of UFPs, researchers undertook a series of controlled exposures in healthy subjects with laboratory-generated BC UFPs. Experiments included exposures for 2 h to three concentrations of 10, 25, and 50 $\mu g/m^3$, with intermittent exercise. Exposure concentration was found to be related to reductions in blood monocytes, basophils, and eosinophils. Expression of adhesion molecules CD54 and CD18 were reduced, whereas lymphocyte expression of activation marker CD25 was increased (Frampton et al. 2006). Other findings of this study at the highest concentration were impaired peak forearm flow during reactive hyperemia and significantly lower venous nitrate levels, whereas there was no difference in venous nitrite levels (Shah et al. 2008). At the lower concentrations of 10 and 25 $\mu g/m^3$, no marked changes in ECG-derived parameters were observed. However, some trends were observed, indicating that some subjects were susceptible (Zareba et al. 2009).

Exposure–dose–response in epidemiological studies of morbidity and mortality

Breitner et al. (2009) and Peters et al. (2009) showed an association between UFP concentrations and daily mortality. They also found that, as air pollution mixtures change (that is, during a period when coal-fired power plants were substituted for gas-fired power plants), the relative strength of the exposure–response function can vary. Exposure to traffic-related PM has been associated with significant adverse cardiovascular health effects (Peters 2009). The efficiency of filters to prevent or reduce such exposure was investigated in controlled experiments involving laboratory-generated UFP as well as ambient traffic-related UFP under two exposure scenarios: one while driving in a car using the in-car recirculation setting and another simulating a workplace where UFP are generated. Results showed that the use of inexpensive, low-efficiency filters reduces UFP concentrations to below levels found in a typical office within 3 min in heavy traffic driving and within 20 min in a UFP production facility. The decrease in deposited dose as a consequence of the reduced exposure will significantly reduce the health risk (Pui et al. 2008).

Peng et al. (2008), in a national multisite time series study of fine and coarse PM, found strong evidence of increased risks of cardiovascular emergency room admissions associated with exposure to coarse PM. However, this effect estimate was no longer statistically significant when adjusted for $PM_{2.5}$. Zanobetti and Schwartz (2009), in another multisite time series study, also found strong evidence of increased risks of overall mortality, cardiovascular, and respiratory-specific mortality associated with ambient exposure to coarse PM. In a study of 26 US communities, Zanobetti et al. (2009a) found that effect estimates for $PM_{2.5}$ total mass and cardiovascular hospital admissions were higher when the $PM_{2.5}$ content of bromine (Br), chromium (Cr), nickel (Ni), or sodium (Na^+) was higher. Correspondingly, Franklin et al. (2008) found that aluminum (Al), silicon (Si), sulfur (S), Ni, and arsenic (As) significantly modified the association between daily $PM_{2.5}$ mass and mortality in 25 US communities. Zanobetti and Schwartz (2006) analyzed hospital admissions data from Boston. This study found associations between MI emergency hospital admissions and BC and between emergency pneumonia admissions and BC, NO_2, and CO. The pattern of associations seen for MI and pneumonia underlines the importance of traffic emissions. Maynard et al. (2007) used geographic information system analysis to assess address-specific exposures to traffic PM for each decedent in Boston. Traffic exposure was associated with all-cause mortality as well as stroke-related and diabetes-related deaths. Sulfate, an indicator of long-range transported particles, was also associated with all-cause mortality risk, but its effect was smaller than that of traffic PM. In a similar study, Bell et al. (2009) found a different set of effect modifiers (BC, V, or Ni). In a multisite time series study of 119 US communities and for the period 2000 to 2005, Peng et al. (2009) found that ambient levels of BC and OC matter, which are generated primarily from vehicle emissions, diesel, and wood burning, were associated with the largest risks of emergency hospitalization across the major chemical constituents of fine particles.

Redox-active chemical components from these sources are enriched on UFP, as discussed in the section on exposure. Cumulative exposure to UFP over a 10.5-year period after the German unification was associated with increased mortality in Erfurt, Germany (Breitner et al. 2009). Relative risks for short-term exposures decreased in parallel with the implementation of air pollution control measures, providing further evidence of causality with level of exposure. Cardiorespiratory mortality was associated with elevated UFP (0.01–0.1 μm) number concentrations with a 4-day lag in Erfurt (Stölzel et al. 2007). No association was found between fine PM mass concentration and mortality.

Eftim et al. (2008) estimated the mortality risks associated with long-term exposure to $PM_{2.5}$ in the same geographical locations as the Harvard Six Cities Study and the ACS Study (Dockery et al. 1993; Pope et al. 1995; Laden et al. 2006). They found a similar exposure–response function. In the National Medicare Cohort Study, Zeger et al. (2008) found strong evidence of an association between 6-year average $PM_{2.5}$ and mortality risk in the east and central part of the USA, but no evidence of an association in the west. Pope et al. (2009) examined changes in life expectancies associated with reductions in $PM_{2.5}$ concentrations in 211 county units in the 51 US metropolitan areas with matching data on fine particulate air pollution for two periods, the late 1970s–early 1980s and the late 1990s–early 2000s. They found that reductions in air pollution accounted for as much as 15 % of the overall increase in life expectancy in the study areas.

Susceptibility

To fully protect public health, we need to characterize variation in risk associated with PM exposure across the population along with the determinants of that variation. For this article, we propose the separate concepts of *vulnerability* and *susceptibility*. Vulnerability refers to factors that increase potential for exposure; susceptibility refers to individual factors that increase risk at any given level of exposure (Fig. 6).

Increased susceptibility implies a greater response at any given level of exposure. Factors associated with increased susceptibility include certain chronic diseases and selected

genotypes. The concept of *environmental justice* is linked to vulnerability, as disadvantaged groups are more likely to have higher exposures.

Research on factors related to susceptibility and vulnerability can help reduce the burden of PM-related adverse health effects. By identifying factors that determine susceptibility, policy makers can make informed decisions to protect susceptible populations as required by the Clean Air Act. In addition, studies of susceptible populations can potentially reveal mechanisms of injury. Given a vulnerable population's high exposure to a variety of pollutants, policy makers must weigh the relative protection afforded by any pollutant-specific strategy.

Genes, diet, and PM susceptibility

Individuals vary greatly in their responses to air pollution exposure. Emerging research is providing insights into the potential role of genes and dietary factors as modifiers of the response to PM. For example, as described by Yang et al. (2008), polymorphisms in oxidative stress genes (NADPH quinone oxidoreductase-1 [NQO-1], GSTM1, and GSTP1) modify responses to PM exposure for various outcomes including respiratory symptoms, lung function, and risk of asthma.

Research has also addressed genetic determinants of various cardiovascular indicators. In the NAS, polymorphisms (C282Y and H63D) in the hemochromatosis (HFE) gene, which modulates uptake of iron and transition metals, were associated with reduced risk for PM-induced alterations in HRV when compared to the wild-type genotype (Park et al. 2006). In the same population, there were significant gene–environment interactions for changes in HRV associated with $PM_{2.5}$ exposure for two oxidative stress genes: GSTM1 and HMOX-1 (Chahine et al. 2007). In a study of ECGs of survivors of MI, prolongation of the corrected QT interval (QTc) associated with PM exposure was modified by NFE2L2, a transcription factor for the glutathione transferase genes (Hampel et al. 2010). EPA-supported investigators found that oxidative stress genetic polymorphisms modified PM effects in the elderly (Chuang et al. 2008).

Promoter SNPs within fibrinogen genes FGA and FGB were associated with modification of the relationship between 5-day averages of PM <10 μm in diameter (PM_{10}) and plasma fibrinogen levels in MI survivors in five European cities (Peters et al. 2009). PM exposures also accelerate the development of atherosclerotic plaque formation in genetically modified apolipoprotein E ($ApoE^{-/-}$) knockout mice (Araujo et al. 2008; Araujo and Nel 2009). In vitro studies with DEP suggest that induction of genes such as HO-1, SELS, NQO-1, and superoxide dismutase 1 (SOD1) by PM exposure could coregulate a large number of genes that are involved in atherosclerosis and vascular injury (Gong et al. 2007).

Diet and genes influencing metabolism may modify the cardiovascular response to air pollution; there is evidence for the potentially protective effects for n-3 fatty acids (Romieu et al. 2005), antioxidants (Sienra-Monge et al. 2004), and dietary methyl nutrients (Baccarelli et al. 2008). In a trial in Mexico, Romieu et al. (2005) have demonstrated the protective effects of antioxidants against lung function reduction and nasal inflammation in children.

Ren et al. (2010b) examined the relationship between PM air pollution and total plasma homocysteine in the VA NAS cohort. Exposure to $PM_{2.5}$ and BC was associated with significant increases in total plasma homocysteine, and there was an indication that this association is modified by the genes GSTT1 and HFE.

Susceptibility during critical stages of the life cycle

The prenatal period and the first year of life are critical developmental periods when air pollution has been posited to influence fetal stress, fetal loss, fetal development, birth outcomes, and subsequent development of chronic cardiovascular, pulmonary, and cognitive dysfunction. Subsequent childhood pollutant exposures may sustain or add to the adverse effects of prenatal and infant exposures. As well as influencing development, pollution may hasten the cardiac, pulmonary, or cognitive decline that comes with aging, and the elderly may be more susceptible to the acute adverse effects of pollution.

Fetal life and early childhood: birth outcomes

Preeclampsia (a source of fetal stress) and preterm delivery were associated with local traffic-generated air pollution in the South Coast Air Basin in California (Wu et al. 2009). Low birth weight and low weight for gestational age were independently associated with increased traffic exposures and

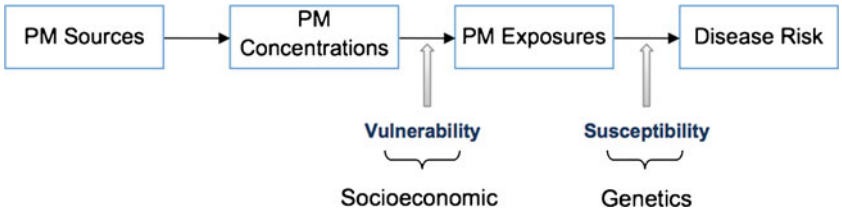

Fig. 6 Framework for vulnerability and susceptibility

community disadvantage in a study of births in Eastern Massachusetts (1996–2002) (Zeka et al. 2008). Two New England studies demonstrated trimester-specific associations of low birth weight with elevated traffic pollution, NO_2, CO, PM_{10}, and $PM_{2.5}$ (Gryparis et al. 2009; Bell et al. 2007b).

Animal model for early life susceptibility to airway development disruption

Children are uniquely susceptible to air pollution insults; they inhale a greater volume per body mass than adults, they spend more time outdoors, and their lungs are still growing and developing. UC Davis investigators exposed juvenile rats to combustion-generated particles in the laboratory (Lee et al. 2008). Early life exposure to ultrafine, high OC/BC particles results in persistent alterations in distal airway architecture that was characterized by an initial decrease in airway cell proliferation (Lee et al. 2010).

Susceptibility in children: neurocognitive outcomes

In a study of children from East Boston, investigators observed associations between BC and decreases in the vocabulary, matrices, and composite intelligence quotient scores of the Kaufman Brief Intelligence Test. Associations also were made between BC and decreases on the visual subscale and general index of the Wide Range Assessment of Memory and Learning (Suglia et al. 2008). An animal model to assess the effects of CAPs and social stress based upon the social dominance paradigm in rats demonstrated that social stress enhanced adverse respiratory and systemic inflammatory outcomes (Clougherty et al. 2010).

Susceptibility in the elderly: subclinical cardiac outcomes

EPA center investigators have shown that the elderly are susceptible to a range of subclinical cardiac outcomes with potential clinical significance; for example, reduced HRV (Luttmann-Gibson et al. 2006; Park et al. 2005). Diet, genes, or medications may modify responses to pollution in the elderly (Park et al. 2005; Ren et al. 2010a, b). Subclinical autonomic, inflammatory, or oxidative stress pollution responses are less consistently detectible in young adults. For example, transient chamber exposure to carbon UFP in concentrations of 10–25 $\mu g/m^3$ did not cause marked changes in ECG-derived parameters in young healthy subjects (Zareba et al. 2009).

Susceptibility in the elderly: blood pressure

Air pollution adversely affects BP even in young healthy individuals (Brook et al. 2009; Urch et al. 2005), but individuals who are elderly or who have preexisting cardiovascular disease or diabetes are at greater risk. In the elderly in the NAS cohort, short-term elevation of estimated resident-specific outdoor BC was associated with postural BP changes (Wilker et al. 2009a); long-term elevation of BC was associated with higher BP. In Medicare enrollees, studies have consistently found increased risks of cardiovascular morbidity and mortality with increases in air pollution (Zeger et al. 2008; Peng et al. 2008).

Susceptibility in the elderly: neurocognitive outcomes

New animal model and human evidence point to a link between air pollution neuroinflammatory and pro-oxidative changes and neurodegenerative disease in the elderly. Studies in OVA-sensitized mice exposed to traffic-related fine particles and UFP showed elevations in proinflammatory cytokines in brain tissue (Campbell et al. 2005). Studies in APOE-deficient mice (rapidly aging and genetically prone to atherosclerosis) exposed to concentrated traffic ultrafine aerosols showed dose-dependent increases in brain tissue proinflammatory cytokines, as well as changes in the activity of cytokine production-related transcription factors (Campbell et al. 2009; Kleinman et al. 2008). In the NAS, increased vehicular traffic (Power et al. 2011) and increased lead (Pb) levels (Weisskopf et al. 2007) have been associated with increased cognitive decline. In adult subjects, investigators found consistent associations between ozone and reduced performance in the Neurobehavioral Evaluation System 2 (Chen and Schwartz 2009).

Preexisting disease as a source of susceptibility to acute and chronic effects of pollution

EPA center studies have contributed to the strong evidence that cardiovascular disease, type 2 diabetes, obesity, chronic obstructive lung disease, and asthma increases the risk of adverse effects of short-term pollution exposures on acute cardiac and pulmonary subclinical and clinical outcomes. Effects of long-term pollution exposure on the development of atherosclerosis and chronic obstructive lung disease are also being studied by EPA-supported animal model and human epidemiologic studies of susceptible adults (for example, the Multi-Ethnic Study of Atherosclerosis and Air Pollution (MESA Air)).

Animal model and in vitro supportive evidence for susceptibility

Autonomic dysfunction has been linked to increased risk of cardiac arrhythmias in humans. Aged spontaneously hypertensive rats, exposed in a mobile laboratory to freshly generated traffic-related aerosols that were dominated by UFPs, showed decreased HR following exposure that was partly

explained by increased parasympathetic tone (Elder et al. 2007). Autonomic tone has also been influenced by pollution in healthy rodents (Pham et al. 2009), but the direction of the effect varies by study. APOE-deficient mice are prone to oxidative stress, inflammation (a known consequence of pollution exposure in in vitro models; Imrich et al. 2007; Xia et al. 2007; Zhao et al. 2009), and the development of atherosclerosis. In the APOE-deficient mouse model, exposure to UFP-dominated traffic aerosols resulted in larger atherosclerotic lesions than exposure to either $PM_{2.5}$ or filtered air (Araujo et al. 2008).

Susceptibility in humans with preexisting cardiac disease

Subclinical outcomes include autonomic control, conduction, repolarization, and arrhythmias. Supporting the clinical observation that increases in ambient particles and traffic exposures may trigger MI within 1 or 2 h (Peters et al. 2004), in a German prospective repeated-measures study of men with coronary artery disease, changes in autonomic nervous system control and repolarization were observed within hours after exposures to particulate pollution (Henneberger et al. 2005). In this same study, increases in atrial and ventricular arrhythmias were seen with 1 to 5 days of cumulative pollution exposure (Berger et al. 2006). Prospective studies in Boston demonstrated changes in autonomic control, including reductions in HRV (Zanobetti et al. 2010), ST segment depression (Zanobetti et al. 2009b), and increases in beat-to-beat variation in the amplitude or shape of the T wave (T wave alternans) (Chuang et al. 2008) with increases in traffic and particle pollution.

Subclinical outcomes include inflammatory, oxidative stress, and hematologic responses. Increased levels of circulating biomarkers of inflammation, antioxidant activity, and platelet activation were associated with primary combustion aerosols in people with coronary artery disease in California (Delfino et al. 2008, 2009, 2010a). In a Rochester panel of postinfarction patients who participated in a cardiac rehabilitation exercise program, decreased HRV and increases in HR turbulence, late repolarization duration, systolic BP, CRP, and fibrinogen were associated with increases in UFP, accumulation mode particle (AMP), and $PM_{2.5}$ concentrations in the previous few hours and days. Associations were more common and parameter estimates generally larger for lagged AMP and UFP concentrations than for $PM_{2.5}$ concentrations (Rich et al. 2012).

Blood pressure

In cardiac rehabilitation patients in Boston, an increase in diastolic and mean arterial BP was associated with higher $PM_{2.5}$ concentrations averaged over the previous 5 days (Zanobetti et al. 2004). Investigators also found traffic pollution-related changes in ambulatory BP in elderly subjects with coronary artery disease, and these associations were stronger in obese subjects (Delfino et al. 2010b).

Susceptibility in humans with preexisting diabetes or metabolic syndrome

Subclinical outcomes include autonomic control, conduction, repolarization, and arrhythmias. Obesity increased the risk of changes in autonomic control (HRV) with short-term increases in $PM_{2.5}$ in the NAS (Schwartz et al. 2005). A North Carolina study of 22 adults with type 2 diabetes showed changes in autonomic control of HR and repolarization, as well as in markers of systemic inflammation and coagulation with short-term increases in ambient $PM_{2.5}$ (Schneider et al. 2010). Within this diabetic population, responses were modified by elevated BMI, elevated glycosylated hemoglobin, and lower adiponectin and GSTM1 variants.

Other subclinical outcomes include inflammatory, oxidative stress, hematologic, and endothelial responses. A repeated-measures study of elders from St. Louis found stronger associations between $PM_{2.5}$ and inflammatory markers such as CRP and IL-6 in the subgroup of individuals with diabetes, obesity, or hypertension (Dubowsky et al. 2006). In the NAS, metabolic syndrome increased the PM_{10} effect on inflammatory markers (Chen and Schwartz 2008). There were increased effects of both $PM_{2.5}$ and BC on sVCAM for obese compared to nonobese subjects (Madrigano et al. 2010). Short-term increases in $PM_{2.5}$, BC, and sulfate (SO_4^{2-}) were associated with increased ICAM-1 and VCAM-1 in a Boston study of people with type 2 diabetes (O'Neill et al. 2007). $PM_{2.5}$, PN, BC, and SO_4^{2-} were each associated with reduced flow-mediated and nitroglycerine-mediated brachial artery dilation among diabetic, but not among nondiabetic, subjects from Boston (O'Neill et al. 2005). Elevation in fine particle exposure was associated with endothelial dysfunction (reduced flow-mediated dilation) in a cohort study of diabetic subjects in North Carolina (Schneider et al. 2008). In people with type 2 diabetes, a controlled clinical inhalation study of a 2-h exposure to 50 $\mu g/m^3$ BC UFP found transient activation of blood platelets, with possible associated activation of blood leukocytes and vascular endothelium (Stewart et al. 2010).

Clinical outcomes

In a 2002 study of four US cities, diabetic people had double the risk of a PM_{10}-associated cardiovascular admission compared with those without diabetes (Zanobetti and Schwartz 2002). There was a 2.0-fold higher mortality risk associated with PM_{10} exposure for diabetics compared to controls in a 2004 case-crossover study (Bateson and Schwartz 2004). PM_{10} effects on mortality were stronger

in diabetics than in nondiabetics in nine Italian cities (Forastiere et al. 2008).

Susceptibility in humans with preexisting asthma and chronic obstructive lung disease

Subclinical outcomes include inflammatory, oxidative stress, and hematologic responses. EPA center investigators have continued their studies of obstructive lung diseases using a number of approaches. A panel study of COPD patients in Erfurt, Germany found an increase in fibrinogen and E-selectin and decrease in vWF with increased pollutant levels. Results for persons with asthma did not differ significantly from non-asthmatics (Hildebrandt et al. 2009). In the same panel, the increase of particulate and gaseous air pollution was associated with multiple changes in the differential white blood cell count in COPD as well (Brüske-Hohlfeld et al. 2010). In a Steubenville panel study, investigators found that elderly participants with COPD were susceptible to pollution effects on pulmonary inflammation, measured as eNO (Adamkiewicz et al. 2004).

Clinical outcomes

PM center investigators have produced strong and consistent evidence (Bateson and Schwartz 2008), as have many other groups worldwide (Holguin 2008; Riedl 2008), that multiple ambient pollutants worsen wheeze and lung function in children and adults with established asthma. Human inhalation and epidemiologic studies (Saxon and Diaz-Sanchez 2000) supported by animal studies (Miller et al. 2009) provide some evidence that air pollution may cause allergy or asthma development. However, findings are still sparse and inconsistent in birth cohort and other epidemiologic studies (Braback and Forsberg 2009; Brauer et al. 2007; Islam et al. 2007; Jerrett et al. 2008; Oftedal et al. 2007; Shankardass et al. 2009). It is not certain whether air pollution is contributing to the resurgence or persistence of airflow obstruction or whether it is a causative factor in asthma development, particularly in longitudinal studies of pollution and asthma development that begin at school age.

Finally, in a PM center study, persons discharged with COPD had pollution-associated mortality risks that were greater than average risks associated with time series analyses (Zanobetti and Schwartz 2009). Investigators found a significant effect of long-term exposure to airborne particles on the risk of death in a large multicity study of elderly subjects discharged alive following an admission for COPD, with a relatively large effect size compared to general population cohorts previously reported. They also found that the effect was not limited to the exposure in each year of follow-up, with larger cumulative effects spread over the follow-up year and three preceding years.

Conclusions

1. The centers developed continued support for the pivotal role of ROS in mechanistic responses and advanced understanding of the hierarchical relationship between adaptive, proinflammatory, and toxic cellular responses in the pulmonary, immune, and cardiovascular systems.
2. Translocations of UFPs to distant sites were important center observations, especially translocation from the upper airway to the brain, a translocation that has potential for long-term adverse effects.
3. Respiratory inflammation resulting from exposures to fine particles and UFP enhanced asthmatic responses in both normal and susceptible animal models in many center studies. In humans, genotype polymorphisms associated with asthma and COPD were related to circulating markers of inflammation, thus further establishing important links between inflammatory responses and these diseases.
4. Center researchers investigated the effects of particle lung deposition on the autonomic nervous system's control of the heart. They also established the importance of traffic-related particles on the development of acute MI, survival after an MI, and influence on the size of an infarct in both human and animal studies.
5. Center studies in experimental animals, humans, and cells in vitro showed adverse effects of fine particles and UFP on the endothelium and vasculature. Such effects included atherosclerotic changes in sensitive animal models and biomarkers associated with vascular disease in people. Because cardiovascular diseases remain important causes of morbidity and mortality, these findings have broad implications for human health.
6. Changes in BP associated with PM exposures have been inconsistent. Center research groups have established that BP is adversely affected by PM exposures and that homeostatic control measures may play an important role in the identification of this adverse response.
7. Center investigators identified the brain and the autonomic nervous system as new targets for adverse effects of PM. Epigenetic mechanisms were recognized as potential explanations for many PM-associated health effects.
8. Center research suggests that PM risk estimates vary across communities and seasons. This heterogeneity is explained in part by the spatial and temporal distribution of sources emissions. Furthermore, BC, OC, and certain metals (V, Ni) may be important source-related components associated with increased PM toxicity.
9. Differences in toxicity of several important PM sources (diesel and gasoline engines, power plants, and

forest fires) have been observed. Center studies have highlighted the importance of atmospheric processes to PM toxicity, noting that SVOCs are important contributors to toxicity and that secondary aerosol formation may enhance PM toxicity.

10. Vehicular traffic is the major contributor to UFP exposures near roadways, and living near a roadway increases the risk for cardiopulmonary disease.
11. Research has demonstrated the value of using particle spatial profiles based on satellite sensing and spatiotemporal models in health effects studies.
12. Exposure–dose–response paradigms depend on dose concentration, particle composition, size fraction, acute or chronic outcome, target organ, and susceptibility factors such as age.
13. Vulnerability (potential for exposure) and susceptibility (factors that increase risk at a given exposure level) are concepts that are critical to environmental policy. Vulnerability and environmental justice are linked, whereas susceptibility includes genetics, comorbid conditions, and age. Center studies in both human populations and animal models have contributed to understanding these relationships.
14. Type 2 diabetes was identified as a leading susceptibility factor in many centers. Center studies have included susceptibilities of fetal, childhood, and elderly life stages to ambient particulate toxicity. Considerable new data continue to strongly support coronary artery disease, asthma, and COPD as primary susceptibility factors.

Future directions

Mechanistic research will continue to be the critical basis for understanding the adverse effects of air pollution. Focus will shift from single components and sources to understanding the effects of multipollutant mixtures. Directions for the continued mechanistic research include both acute and long-term studies focusing upon inflammatory responses in the lung, systemic vasculature, heart, and brain. Identification of new biomarkers and outcomes will be key for epidemiological studies. Identification of genetic and epigenetic mechanisms as critical intermediate steps in responses to multipollutant mixtures will be important, as will the development of new measures of toxicity. Enhancing our knowledge in defining the steps from inhalation to specific biological outcomes will continue to be a primary goal. Data generated from the EPA centers are needed to support the revision and development of air quality standards in the USA and throughout the world.

Exposure research should continue its focus upon sources of pollutant exposure, local exposure differences, and formation of secondary particles formed within the multipollutant atmosphere. Satellite sensing and spatiotemporal models will play key roles in health effects studies. Defining exposure–dose–response relationships will remain the basis of support of EPA's mission to protect health. During the past 5 years, center investigators have begun to elucidate the relationship between increased susceptibility, genes, and environment and have demonstrated that polymorphisms in oxidative stress genes can modify responses to PM exposure for various cardiovascular and respiratory outcomes. Areas of future susceptibility research are likely to include pregnancy and pregnancy outcomes such as birth weight and prematurity; neurological diseases, given our increasing understanding of transport of particles to the brain; and perhaps systemic diseases such as lupus and rheumatoid arthritis that are characterized by alterations in immune function.

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